S119 Epidemiology and current clinical challenge of tuberculosis

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The world is currently facing a widespread tuberculosis epidemic. According to the World Health Organization, more than 1.8 billion people are infected with *Mycobacterium tuberculosis* worldwide. The current prevalence of active tuberculosis is more than 22 million, and each year at least 8 million new cases will occur as well as 3 million deaths. Therefore, between 1990 and 2000, more than 30 million people will die from tuberculosis—more than ever before within a decade. More than 90% of all new cases and deaths occur in developing countries, which are struggling under the enormous economic burden induced by this single disease. Most cases can be observed in Sub-Saharan Africa and South-East Asia. In both these regions, infection with HIV is also endemic, resulting in a 14% infection rate in all TB cases. Moreover, tuberculosis is still the main cause of death in HIV-positive people. To make things worse, we are observing a growing number of resistant *M. tuberculosis* strains worldwide (e.g. 6.6% single drug resistance in previously untreated patients and 13% multidrug resistance in patients with a history of previous antituberculous therapy). Therefore, the main challenges for the coming years are the implementation of sufficient TB-control programs worldwide and the battle against resistance. However, without strong financial support from the developed countries, we will not achieve this goal.

Mycobacterial diseases

S121 Genetics of drug resistance in mycobacteria

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While the global magnitude of the multidrug-resistant tuberculosis (MDR-TB) problem is not well known, gaining insight into the mechanisms of resistance and into the pathogenicity and transmissibility of MDR-TB will be important for future control of the disease. Mutations in the *katG*, *inhA*, *ahpC* and *kasA* genes are found in 75–90% of isoniazid-resistant strains, and rifampin resistance is associated with *rpoB* mutations (95%). Genetic information is also available for pyrazinamide (*pncA*, *fasI*), ethambutol (*embB*), streptomycin (16S rDNA and *rpsL*), clarithromycin (23S rDNA), amikacin–kanamycin (16S rDNA), and the fluoroquinolones (*gyrA*, *gyrB*, *lfrA*). At a practical level, these data allow the development of novel resistance testing methodologies, and may permit better design of MDR-TB treatment strategies. Mutation analysis may assist in the assessment of the pathogenicity of MDR-TB strains. In the future, knowledge of the molecular mechanisms of action of antituberculous drugs, the availability of the complete tuberculosis genome sequence, together with protein structural information and combinatorial chemistry, may lead to new drugs.

S122 Vaccination strategies for tuberculosis

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Tuberculosis constitutes a major global health threat. Although BCG represents a vaccine capable of conferring protection against childhood tuberculosis, it fails to provide sufficient protection against the most prevalent form of the disease, adult pulmonary tuberculosis. Thus, novel vaccination strategies against tuberculosis are urgently required. Tuberculosis is a chronic infectious disease caused by *Mycobacterium tuberculosis*, which is capable of persisting in macrophages. Acquired resistance depends on multiple T-cell populations, comprising not only CD4 T-cells but also CD8 T-cells and unconventional T-cells. Activation of mycobactericidal mechanisms in macrophages by interferon-gamma and other cytokines from T-cells is crucial for controlling the pathogen. In addition, other T-cell functions are required for optimal protection. Thus, any future vaccine has to mobilize the most appropriate combination of T-cells needed for control of *M. tuberculosis* in the host. From an immunologic standpoint, BCG may fail to induce the appropriate combination of T-cells and/or lack protective antigens. Vaccine strategies currently pursued include: secreted antigens in adjuvant; naked DNA; recombinant bacterial or viral vaccine carriers expressing specific antigens of *M. tuberculosis*; *M. tuberculosis* deletion mutants; improved recombinant BCG capable of stimulating the appropriate T-cell combination and expressing unique antigens of *M. tuberculosis*. The potential advantages and disadvantages of these different vaccine candidates will be discussed.

S123 Progress in antimycobacterial treatment

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The five standard 'first-line' antimycobacterial agents used for the treatment and prevention of *Mycobacterium tuberculosis* disease were developed well over a quarter of a century ago: streptomycin (1944), isoniazid (1952), pyrazinamide (1952), ethambutol (1961), and rifampicin (1966). Since then, the development of truly novel compounds that would significantly add to the available therapeutic armamentarium has been disappointingly slow, especially in view of the well-publicized outbreaks of multidrug-resistant tuberculosis (MDR-TB) and the identification by WHO/IUATLD of numerous 'hot-spots', regions of the world where there is an alarmingly high prevalence of MDR-TB. Current new drugs of interest are the following.

Fluoroquinolones. Several fluoroquinolones, which have become the most important 'second-line' antituberculosis drugs, are available, although thorough clinical comparisons are scarce. Because of its apparent safety and good activity, levofloxacin may be the agent of choice. Sparfloxacin is also effective against *M. tuberculosis*, but phototoxicity is a problem in 10% of recipients (may be lower in dark-skinned persons). Because of its anti-*M. tuberculosis* activity, moxifloxacin is an interesting new compound.

Macrolides. No macrolide antibiotics with significant in vitro activity against *M. tuberculosis* have been identified. In contrast, clarithromycin has been shown to be effective in the treatment of disseminated *Mycobacterium avium* complex (MAC) disease, and both clarithromycin and azithromycin have been approved in the USA for prophylaxis against MAC.

Rifamycin derivatives. Rifabutin is approved in the USA for prophylaxis against MAC and is used in several countries for the treatment of tuberculosis. It has substantial cross-resistance with rifampicin, but because of relatively little bidirectional drug interaction with indinavir, the CDC has recommended that rifabutin be used in place of rifampicin in the treatment of HIV-infected tuberculosis patients for whom an HIV protease inhibitor is indicated. Rifapentine is of considerable interest because of its long half-life and the possibility of once-weekly dosing; a phase III trial is now underway and experimental studies suggest that the combination of rifa-

pentine and isoniazid, once weekly for 3 months, provides highly effective chemoprophylaxis.

Other agents: Information about *in vitro* and to a lesser extent *in vivo* activities of two oxazolidinone compounds (U-100592 and U-100766) and a nitroimidazole compound (PA-824) suggest a possible future role for one or more of these agents.

In conclusion, development of effective new antimycobacterial agents has lagged far behind the need for them. Improved public–private sector collaboration is needed to remedy the deficiency.

Clinical implications of antibiotics resistance in developing countries

S126 Use and misuse of antibiotic policies to control drug resistance

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The use of antibiotics has led to the emergence of a variety of resistant bacteria which have clearly added to the challenge of controlling infections with new agents.

Misuse of antibiotics is responsible for a general pool of resistant strains in the population where there is unrestricted sale of antibiotics, i.e. over the counter.

Appropriate use of antibiotic policies to control drug resistance should be encouraged and implemented. In order to do so, an antibiotic committee should be responsible for the formulation and supervision of an antibiotic policy.The policy will improve patient care by considered use of antibiotics for prophylaxis and therapy, make better use of finance, retard the emergence of multiple antibiotic-resistant bacteria and improve education of junior doctors by providing guidelines for appropriate therapy.

The antibiotic committee will have to make rational choices among equivalent antibiotics and classes of drugs in order to select the least expensive, most effective agents.Cost should determine the selection when microbiological, pharmacologic and other relevant properties are similar.

Data on antibiotic susceptibility of bacterial isolates from the local area will assist the committee in producing effective guidance for the patient population.The laboratory should give data on the extent of resistance to a particular antibiotic. When no local microbiology laboratory exists, the antibiotic policy should be based upon a basic formulary; when resources for microbiology are scarce, priority should be given to examination of samples from nosocomial life-threatening cases.

Inappropriate use of antibiotic policies has limited the choice of antibiotics, and there is a need for more prudent use of antibiotics in the treatment of infections, especially in developing countries.

S127 The clinical relevance of antibiotic resistance for the management of pneumonia in developing countries

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There is now widespread in vitro resistance to the common drugs used for the management of pneumonia in developing countries. Data from both developed and developing countries, however, show that more than 99% of pneumococci identified as penicillin resistant in the laboratory can be treated by adequate intravenous doses of penicillin or ampicillin. Trimethoprim–sulfamethoxazole is less active than amoxycillin for the management of severe pneumonia in developing countries, The lesser activity of trimethoprim–sulfamethoxazole was not directly related to levels of antimicrobial resistance to that agent, suggesting that amoxycillin is intrinsically more active against the common bacterial agents causing pneumonia. Macrolide resistance has emerged as a major problem in Asia, with 80% of pneumococci isolated from children in China exhibiting resistance to this class of agent. Guidelines for the management of pneumonia recommend that the breakpoints for penicillin resistance should be increased, so that clinicians are not faced with dilemma of treating 'resistant' strains with penicillin. Nasopharyngeal screening programs give data on antimicrobial resistance that are comparable to those obtained from sterile-site specimens. More data are required on the impact of penicillin resistance on the oral management of pneumonia. Current data would suggest that, where affordable, oral amoxycillin should replace trimethoprim–sulfamethoxazole as the drug of choice for the management of moderate to severe pneumococcal pneumonia in developing countries.

Short course antibiotic therapy with macrolides

S128 Risk–benefit of short-course therapy with macrolides

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Due to favorable pharmacokinetics, shorter therapeutic regimens are now used with some of the newer macrolides. These products are characterized by rapid and substantial intracellular accumulation, particularly in the lysosomes, followed by slow release from the cells, so that intracellular concentrations can surpass blood concentrations by several hundred-fold. Among macrolides, azithromycin displays the most important intracellular accumulation, making possible simplified dosing. Most macrolide-susceptible respiratory tract infections can be efficiently treated by once-a-day dosing for 3 days with azithromycin; genital and eye infections caused by *Chlamydia trachomatis* are controlled with a single dose of the drug. There is a trend to extend the concept of a single therapeutic dose in respiratory infections, more particularly in acute otitis media and pharyngitis, with the same total dose as in the more conventional treatment (30 mg/kg for a child). Compared to the 3-day regimen, the single dose assures the same serum half-life and AUC, but maximum antibiotic concentrations appear earlier (at day 1 versus day 3) and reach higher levels. In theory, this could provide improved efficacy and limit the risk of resistance selection. The single dose could lead to 100% compliance if the drug is taken in presence of heath personnel. Improved compliance decreases the risk of therapeutic failure and the cost. Possible inconvenience includes more side effects associated with drug concentrations, particularly the gastrointestinal manifestations.

S129 Overview of azithromycin therapy

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Azithromycin (AZ) has proven in vitro bacteriologic activity against many important community-acquired Gram-positive and Gram-negative pathogens, as well as the atypical respiratory pathogens. In